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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/521,053

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EXAMINER

DAVIS, MINH TAM B

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/521,053	Applicant(s) PHILIPS ET AL.	
	Examiner MINH-TAM DAVIS	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 February 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 43-60 and 62-80 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 43-60, 62-80 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|----------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>2/4/09</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant cancels claims 61, 81.

Accordingly, claims 43-60, 62-80, a method for treating central nervous system cancer or glioma cells, using an antibody to SEQ ID NO:2, are examined in the instant application.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-81 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for reasons already of record in paper of 11/06/08.

1. Claims 43-60, 62-80 are rejected under 112, first paragraph, for lack of enablement for a method for treating central nervous system cancer or glioma, using an antibody to SEQ ID NO:2.

The response asserts as follows:

The Examiner cites a variety of unrelated documents, most of which are not relevant to the issue of enablement in the present case, since they are outdated (published 8-6 years before the priority date of the present application) and/or concern approaches to cancer treatment, such as cancer vaccines, that are entirely different from the approach disclosed and claimed in the present application. Furthermore, most arguments advanced by the Examiner do not specifically

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address the question while the particular methods claimed in the present application, as opposed to cancer treatment in general, would not be expected to work. Indeed, the efficacy of therapeutic antibodies is clearly demonstrated by the wide-spread successful use of antibody therapy in the treatment of a variety of cancers, including severe, aggressive forms of cancer, and the fact that currently there are twenty-one FDA approved therapeutic monoclonal antibodies in the U.S. market and hundreds of more are undergoing clinical trials. The fact that not all clinical trials are successful is irrelevant for the assessment of patentability, since the legal standard for assessing patentability is not absolute certainty rather preponderance of evidence.

The response has been considered but is not found to be persuasive for the following reasons:

The unpredictability of cancer immunotherapy, as taught by the cited references of White et al, Boon, Kirkin et al, Smith et al, Bodey et al, Lee et al, Kaiser, Gura, and Ezzell, although some are published 8-6 years before the priority date of the instant application, applies as well to the claimed immunotherapeutic method. For example, Bodey et al, 2000, of record, teach that although general immune activation against the target antigens has been documented in most cases, reduction of tumor load has not been frequently observed in human patients (abstract, second column, p.2673). Bodey et al teach that the failure of cancer vaccine is due to natural selection of highly aggressive clones in the treated patient, said clones no longer express the cancer specific antigen (abstract, second column, p.2673). Bodey et al teach that these clones of tumor cells survive the immune system, through secretion of immunoinhibitory cytokines, downregulation of MHC, loss of costimulatory molecules, and induction of T cell anergy (p.2673, second column, last paragraph). Such unpredictability of cancer immunotherapy also is

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confirmed by recent articles, for example, by Mellman, 2006, *The Scientist*, 20(1): 47-56, and Kaiser, 2006, of record. Mellman teaches that immunotherapy of cancer has yet to live up to expectations (p.47). Mellmann teaches that attempts at using cytokines to stimulate anticancer T cells, or deploying toxin-conjugated antibodies as magic bullets were never quite successful, and that therapeutic vaccines for cancer have proven similarly disappointing (p.47). Kaiser (*Science*, 2006, 313, 1370) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para. Moreover, the following unpredictability applies as well to the claimed method, such as: 1) whether the antigen expression or presentation by glioma cells is consistent, in view of the teaching of Boon et al, and 2) whether the expressed antigen is present on all or near all glioma cancer cells to allow effective targeting, and to prevent a subpopulation of antigen-negative cells from proliferating, in view of the teaching of White et al. Similarly, one cannot predict whether excess shed antigen in circulation due to antigen overload, as taught by White et al, and Boon, would not bind to most of the administered antibodies, and thus blocking their access to glioma cells through blood brain barrier, such access is already hampered by blood brain barrier.

Moreover, although some antibodies have been approved by FDA for treating certain cancers, different antibodies have different properties. Because of this, one cannot predict whether the claimed antibody could be used successfully for treating glioma or central nervous system cancer.

The response submits the references by Huang et al, 2006, 2008, Nomura et al, 2007, Yang et al, 2007, which teach treatment prostate cancer, renal cell carcinoma and myeloma, respectively, using anti-beta-microglobulin antibody. The response asserts that this post-

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published evidence confirms that antibodies to TAT4434 of SEQ ID NO: 2 (beta2-microglobulin) effectively kill cancer cells expressing beta2-microglobulin. The response asserts that this, coupled with the experimental data disclosed in the present application, clearly enables the killing of central nervous system cancer cells that express such polypeptide (e.g. glioma cells), and the treatment of tumors comprising such cells, as claimed in the present application. The response asserts that this is true despite difficulties associated with delivery of drugs through the blood-brain barrier, since various approaches for drug delivery through the blood-brain barrier, such as osmotic and biochemical means, and the use of vasoactive substances, are well known in the art.

The submission of Huang et al, 2006, 2008, Nomura et al, 2007, Yang et al, 2007 is acknowledged.

The response has been considered but is not found to be persuasive for the following reasons:

Although antibodies to the claimed antigen could be used for treating prostate cancer, renal cell carcinoma and myeloma, one cannot predict whether the claimed antibodies could be used for treating central nervous system cancer or glioma, because different cancers have different properties and cannot be predicted to response to the same drug. For example, prostate cancer, renal cell carcinoma and myeloma do not have the problem with drug delivery through brain barrier, which problem is further exacerbated by the use of the claimed antibody with increased binding to FcRn, in view of the teaching of Roopenian et al, of record. Roopenian et al teach that unlike the endothelium in other organs, the cerebral vascular endothelial cells are joined by tight junctions that prevent the passive diffusion of macromolecules across the blood-

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brain barrier in the absence of specific transporter (p.719, first column, last paragraph).

Roopenian et al teach that vascular endothelium, including those in the brain, are the main sites that express FcRn (p.717, first column, third paragraph). Roopenian et al teach that rather than transporting IgG into the CNS, **FcRn mediates reverse transport of IgG into the circulation from the brain**, as shown for IgG injected into the brain parenchyma (p.719, second column, first paragraph). Further, one cannot predict whether the claimed particular glioma or central nervous system cancer cells would not have the following problems with the claimed antigen: 1) inconsistency in antigen expression or presentation by tumor cells, as taught by Boon et al, and 2) whether the expressed antigen is present on all or near all cancer cells to allow effective targeting, and to prevent a subpopulation of antigen-negative cells from proliferating, as taught by White et al.

Moreover, the response does not have any evidence that approaches for drug delivery through the blood-brain barrier, such as osmotic and biochemical means, and the use of vasoactive substances could solve the problem with using an antibody with increased binding to FcRn, which FcRn mediates reverse transport of IgG into the circulation from the brain.

Further, even if an antibody to SEQ ID NO:2 could be successfully used to treat glioma, one cannot predict that **cancers in the central nervous system** other than glioma would be successfully treated using an antibody to SEQ ID NO:2, because one cannot predict that these cancers overexpress SEQ ID NO:2, which overexpression is necessary for targeting the antibody to the cancer cells.

In addition, one would not know how to practice the claimed method, because it not clear what constitutes the "**corresponding normal cells**".

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2. Claims 43-60, 62-80 are also rejected under 112, first paragraph, for lack of enablement for a method for treating central nervous system cancer or glioma, that overexpresses a polypeptide having **at least 80% identity to SEQ ID NO:2**.

The response asserts that the rejection is obviated, because the claims, as currently amended, cover methods targeting variants of SEQ ID NO: 2 which are overexpressed in central nervous system or glioma cancer cells relative to corresponding normal cells.

The response has been considered but is not found to be persuasive for the following reasons:

One cannot predict that central nervous system or glioma would overexpress the at least 80% variant of SEQ ID NO:2, in view of the teaching of Schmid et al, Conner et al, of record, that variants of a sequence do not necessarily express at the same level as the corresponding wild type.

3. Claims 56-59, 76-79 are also rejected under 112, first paragraph, for lack of enablement for making **an antibody that has increased binding to FcRn, having any modification of amino acids as recited in claims 56 or 76**.

The response asserts as follows:

Methods for generation of amino acid variants at the indicated positions of an antibody Fc region, such as targeted random mutagenesis, were well known in the art at the priority date of the present application. Similarly, methods for assessing the binding of such variants to FcRn, such as competitive FACS binding assays, were well known, along with methods for measuring the half-life of antibodies comprising such alteration within their Fc region. Based on this

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teaching and general knowledge in the art at the priority date of the present application about effector function engineering of antibodies, one of ordinary skill in the art would have been able to engineer the effector function of the antibodies used in the methods of the present invention by amino acid alterations at one or more positions recited in the claims, without undue experimentation. It is noted that the fact that some, or even extensive, experimentation might be necessary, should not lead to the finding of lack of enablement, if it is of routine nature, as it is in the present case.

The response has been considered but is not found to be persuasive for the following reasons:

Shields et al, of record, specifically teach that modification some of the amino acids as claimed in claim 56 or 76 result in abrogation or reducing binding to FcRn, and not increased binding to FcRn as claimed.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

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the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS

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April 19, 2009

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643